

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Jeroen M. Bezemer et al. )  
Serial No.: TBA ) Examiner:  
Filed: Herewith ) Art Unit:  
Title: MOLDING OF A POLYMER )

Assistant Commissioner for Patents  
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Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Preliminary to examination, please amend the application being submitted herewith as follows.

In the Specification:

On page 1, after the title and before the first paragraph, please insert the following paragraph:

--This application is a continuation of prior international application no. PCT/NL00/00554, filed 4 August 2000; which claims priority from European Patent Application No. EP 99202599.9, filed 6 August 1999.--

On page 1, lines 4, 5, 12 and 34, replace "terephthalate" with --terephthalate--.

On page 2, lines 12, 18, 33, and 35, replace "terephthalate" with --terephthalate--.

On page 3, lines 3, 5, 27, 32, 33, 34, and 35, replace "terephthalate" with --terephthalate--.

On page 3, line 27, remove the extra space between "-OLO-CO-Q-CO-" and "," on line 28.

On page 4, lines 1, 2, 8, 29, and 31, replace "terephthalate" with --terephthalate--.

On page 5, line 26, insert --°-- after "20".

On page 5, line 27, insert --°-- after “30”.

On page 7, line 10, insert --,-- after “hormones”.

On page 10, line 10, replace “flurohydrocortisone” with --fluorohydrocortisone--.

On page 11, lines 20 and 22, replace “terephthalate” with --terephthalate--.

On page 14, line 16, insert a new paragraph before “*Antitoxins:*”

On page 17, line 25, replace “terephthalate” with --terephthalate--.

After page 20, on new page 21, please insert the following title and paragraph:

--ABSTRACT OF THE DISCLOSURE

The invention relates to a process for molding a copolymer of a polyalkylene glycol terephthalate and an aromatic ester, comprising the steps of: a) preparing a solution of the copolymer in a suitable first solvent; and b) forming a gel of the solution.--

New page 21 of the application with the abstract is also being herewith submitted.

In the Claims:

In claim 1, line 1, replace “terephthalate” with --terephthalate-- as follows:

1. (Amended) A process for molding a copolymer of a polyalkylene glycol terephthalate and an aromatic ester, comprising the steps of
  - a) preparing a solution of the copolymer in a suitable first solvent; and
  - b) forming a gel of the solution.

In claim 3, line 10, insert --to-- before “claim 1” and delete “or 2”; and on line 11 insert --°-- before “20” as follows:

3. (Amended) A process according to claim 1 wherein the solution is prepared at a temperature of 20° - 200°C.

In claim 4, line 12, delete “any of the preceding claims” and substitute --claim 1-- as follows:

4. (Amended) A process according to claim 1, wherein the solution comprises between 5 and 90 wt.%, based on the weight of the solution, of the copolymer.

In claim 5, line 15, delete "any of the preceding claims" and substitute --claim 1-- as follows:

5. (Amended) A process according to claim 1, wherein an additive is added to the solution, which additive is chosen from the group of calcium phosphates and biologically active agents.

In claim 6, line 19, delete "any of the preceding claims" and substitute --claim 1-- as follows:

6. (Amended) A gel obtainable by a process according to claim 1.

In claim 7, line 21, delete "any of claims 1-5" and substitute --claim 1-- as follows:

7. (Amended) A process according to claim 1, wherein the gel is placed in a second suitable solvent to obtain a solid body of the copolymer.

In claim 9, line 27, delete "or 8" as follows:

9. (Amended) A process according to claim 7, wherein the gel is placed in an amount of at least 300 vol.%, with respect to the volume of the gel, of the second solvent.

In claim 10, line 30, delete "any of claims 1-6" and substitute --claim 1-- as follows:

10. (Amended) A process according to claim 1, wherein the gel is freeze-dried to obtain a solid body of the copolymer.

In claim 11, line 33, delete "claims 7-10" and substitute --claim 7-- as follows:

11. (Amended) A solid body obtainable by a process according to claim 7.

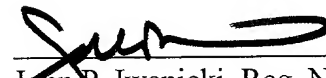
In second, misnumbered claim 11 on page 20, line 1, please change the claim number to --12-- as follows:

12. (Amended) The use of a solid body according to claim 10 as a scaffold for tissue engineering or a bone filler cement.

Applicants respectfully request entry and consideration of the amendments.

Respectfully submitted,

Date: January 15, 2002



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## Version of Amendments with Markings to Show Changes Made

### In the Specification:

On page 1, paragraphs 1, 2 and 5:

The invention relates to a process for molding a polymer. More in particular, the invention relates to a process for molding a Copolymer of a polyalkylene glycol terephthalate and an aromatic ester.

Copolymers of a polyalkylene glycol terephthalate and an aromatic esters have been found to possess highly favorable properties, such as biodegradability and biocompatibility. For these reasons, they are finding application in tissue engineering applications, such as in the function of scaffolds for seeding cells of different types. Particularly, copolymers of polyethylene glycol terephthalate (PEGT) and polybutylene terephthalate, which are known under the name of Polyactive®, have been found to give promising results in this regard.

On page 2, paragraphs 2, 3, and 7:

Further, in particular in view of the above referred to applications of the copolymers it is often desired to be able to incorporate (bioactive) additives in the solid bodies to be formed. For instance, the presence of growth factors may be very much desired in order to enhance cell growth or differentiation. As many of these bioactive additives are very sensitive compounds the need for working under mild conditions becomes even more important. it is thus a further object of the invention to provide a method for molding a copolymer of a polyalkylene glycol [terephthalate] terephthalate and an aromatic ester under mild conditions, which method can conveniently be adapted in order to incorporate additives into the solid body to be formed.

Surprisingly it has now been found that the properties of copolymers of a polyalkylene glycol [terephthalate] terephthalate and an aromatic ester make it possible to produce solid bodies of them in a gel molding process. Accordingly, the invention relates to a process for molding a copolymer of a polyalkylene glycol [terephthalate] terephthalate and an aromatic ester, comprising the steps of:

The copolymer which is formed into a solid body according to the invention, is a copolymer of a polyalkylene glycol [terephthalate] terephthalate and an aromatic polyester.

Preferably, the copolymer comprises 20-90 wt.%, more preferably 40-70 wt.% of the polyalkylene glycol [terephthalate] terephthalate and 80-10 wt.%, more preferably 60-30 wt.% of the aromatic polyester. A preferred type of copolymers according to the invention is formed by the group of block copolymers

On page 3, paragraphs 2, 4, and 5 and page 4 paragraph 1:

The polyalkylene glycol [terephthalate] terephthalate may have a weight average molecular weight of about 150 to about 4000. Preferably, the polyalkylene glycol [terephthalate] terephthalate has a weight average molecular weight of 200 to 1500. The aromatic polyester Preferably has a weight average molecular weight of from 200 to 5000, more preferably from 250 to 4000. The weight average molecular weight of the copolymer preferably lies between 10,000 and 300,000, more preferably between 40,000 and 120,000.

In a preferred embodiment, the polyalkylene glycol [terephthalate] terephthalate component has units of the formula -OLO-CO-Q-CO-, wherein O represents oxygen, C represents carbon, L is a divalent organic radical remaining after removal of terminal hydroxyl groups from a poly(oxyalkylene)glycol, and Q is a divalent organic radical.

Preferred polyalkylene glycol [terephthalates] terephthalates are chosen from the group of polyethylene glycol [terephthalate] terephthalate polypropylene glycol [terephthalate] terephthalate, and polybutylene glycol [terephthalate] terephthalate and copolymers thereof, such as poloxamers. A highly preferred polyalkylene glycol [terephthalate] terephthalate is polyethylene glycol [terephthalate] terephthalate.

On page 5, paragraph 2:

In accordance with the invention, the copolymer is first dissolved in a suitable solvent, by which is meant that a substantially homogeneous, one phase mixture is prepared of the copolymer and said suitable solvent. Depending on the nature of the copolymer and the solvent, it may be necessary to work at elevated temperature in order to dissolve the copolymer. However, the temperature required for this step will always be low in comparison with the temperature that would be needed to prepare a melt of the copolymer. Thus, the present process allows the molding of the copolymer under mild conditions. Suitable temperatures for preparing

the solution will be below the boiling temperature of the solvent, preferably between 20° and 200°C, more preferably between 30° and 100°C.

On page 7, paragraph 2:

The term "biologically active agent", as used herein, means an agent which provides a therapeutic or prophylactic effect. Such agents include, but are not limited to, antimicrobial agents (including antibacterial and anti-fungal agents), anti-viral agents, anti-tumor agents, hormones, immunogenic agents, growth factors, lipids, and lipopolysaccharides.

On page 10, line 10:

16.1.1 *Mineralocorticosteroids*: cortisol, desoxycorticosterone, [flurohydrocortisone] fluorohydrocortisone

On page 11, paragraph 6 at line 18:

When a non-peptide, non-protein, small-sized drug, such as those described above, is to be incorporated, the polyalkylene glycol [terephthalate] terephthalate component of the copolymer preferably has a molecular weight of from about 200 to 400. Also, the polyalkylene glycol [terephthalate] terephthalate component is present in the copolymer in an amount of from 20 wt.% to 90 wt.% of the weight of the copolymer, preferably from about 40 wt.% to about 70 wt.% of the weight of the copolymer. In general, the aromatic polyester is present in the copolymer in an amount of from 10 wt.% to 80 wt.% of the copolymer, preferably in an amount of from about 30 wt.% to about 60 wt.% of the copolymer.

On page 14, line 16, insert a new paragraph beginning with "*Antitoxins*:"

*Antitoxins*: Botulinum antitoxin, diphtheria antitoxin, gas gangrene antitoxin, tetanus antitoxin.

On page 17, paragraph 5 at line 24:

In a beaker, 100 grams of a copolymer of polyethylene glycol [terephthalate] terephthalate (PECT,  $M_w = 1148$ ) and polybutylene terephthalate (PBT), wherein the weight ratio of PEGT to PBT was 60 to 40, were dissolved in 200 ml N-methylpyrrolidone (NMp) at a temperature of

100°C by manual stirring. After approximately 30 minutes, a homogeneous solution was obtained.

In the Claims:

1. (Amended) A process for molding a copolymer of a polyalkylene glycol [terephthalate] terephthalate and an aromatic ester, comprising the steps of

- a) preparing a solution of the copolymer in a suitable first solvent; and
- b) forming a gel of the solution.

3. (Amended) A process according to claim 1[or 2] wherein the solution is prepared at a temperature of 20° - 200°C.

4. (Amended) A process according to [any of the preceding claims] claim 1, wherein the solution comprises between 5 and 90 wt.%, based on the weight of the solution, of the copolymer.

5. (Amended) A process according to [any of the preceding claims] claim 1, wherein an additive is added to the solution, which additive is chosen from the group of calcium phosphates and biologically active agents.

6. (Amended) A gel obtainable by a process according to [any of the preceding claims] claim 1.

7. (Amended) A process according to [any of claims 1-5] claim 1, wherein the gel is placed in a second suitable solvent to obtain a solid body of the copolymer.

9. (Amended) A process according to claim 7 [or 8], wherein the gel is placed in an amount of at least 300 vol.%, with respect to the volume of the gel, of the second solvent.

10. (Amended) A process according to [any of claims 1-6] claim 1, wherein the gel is freeze-dried to obtain a solid body of the copolymer.



11. (Amended) A solid body obtainable by a process according to [claims 7-10] claim 7.

[11.] 12. (Amended) The use of a solid body according to claim 10 as a scaffold for tissue engineering or a bone filler cement.

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